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Health and Environmental Effects Profile for 1,1-Dimethylhydrazine

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 1,1-DIMETHYLHYDRAZINE

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16. ABSTRACT

The Health and Environmental Effects Profile for 1,1-dimethylhydrazine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 1,1-Dimethylhydrazine has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for 1,1-dimethylhydrazine is 8.7 $(mg/kg\ bw/day)^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

BSP	Bromsulphalein
BUN	Blood urea nitrogen
CNS	Central nervous system
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
SAAM	Standard algal assay medium
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Synonyms for 1,1-dimethylhydrazine include unsymmetrical dimethylhydrazine, UDMH, UNS-dimethylhydrazine, asymmetrical dimethylhydrazine, N,N-dimethylhydrazine, dimazine and dimethylhydrazine (IARC, 1974). 1,1-Dimethylhydrazine will be referred to as 1,1-DMH throughout this profile. The structure of 1,1-DMH is given below:

$$(CH_3)_2\text{-}N\text{-}NH_2$$

Molecular Formula: $C_2H_8N_2$

Molecular Weight: 60.1

The Chemical Abstracts Service (CAS) Registry Number for 1,1-DMH is 57-14-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,1-DMH is a clear, colorless, flammable, hygroscopic liquid at ambient temperature (IARC, 1974). It has an ammonia-like fishy smell that is characteristic of alkyl hydrazines, fumes in air and gradually turns yellow. Some of the physical and chemical properties of 1,1-DMH are given below (IARC, 1974):

Boiling point:	63°C
Melting point:	-57°C
Specific gravity (25°C)	0.782
Vapor Pressure:	157 mm Hg at 25°C (NIOSH, 1978)
Solubility:	miscible with water

1.3. PRODUCTION DATA

The 1977 TSCA inventory lists four producers of 1,1-DMH. The only production volume indicated was for the Naval Sea Systems Command (100,000-1,000,000 pounds/year). NIOSH (1978) reported that ~1-2 million pounds are produced annually for use in rocket propulsion. While several other uses

are reported in Section 1.4., the volume used in each of them is unknown. At present, Uniroyal, Inc. (SRI, 1982) and Olin Corp. (USITC, 1981) appear to be the only United States producers of this compound. 1,1-DMH is made commercially by Uniroyal by the reductive catalytic alkylation of hydrazide (probably acetic acid hydrazide) with formaldehyde and hydrogen, followed by basic hydrolysis of acetic acid dimethylhydrazide to remove the acetyl group (Schiessl, 1980).

1.4. USE DATA

1,1-DMH is predominately used as a high-energy fuel in military applications (Tuazon et al., 1982). It may be used individually or in mixtures with hydrazines and/or monomethyl hydrazine as a rocket propellant and fuel for thrusters and small electrical power generating units. A 50-50 mixture of hydrazine and 1,1-DMH (Aerozine-50) is used, for example, as fuel for the Titan II missile, and the Space Shuttle system currently uses these fuels in large quantities. Significant quantities of 1,1-DMH are used in the manufacture of N-dimethylaminosuccinamic acid, a plant growth regulator (IARC, 1974). 1,1-DMH is also used in chemical synthesis, in photographic chemicals, as a stabilizer for organic peroxide fuel additives and as an adsorbent for acid gases (NIOSH, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

1,1-DMH can be released to the atmosphere during use (e.g., residual rocket fuel), and from spills, leaks and venting during loading, transfer and storage. It appears that rapid reaction with ozone and hydroxyl radicals will be the major fate of 1,1-DMH in the atmosphere. 1,1-DMH does not photolyze in the solar actinic region (λ >290 nm) (Tuazon et al., 1981).

Studies in which 2-16 ppm concentrations of 1,1-DMH were mixed with similar levels of ozone under dark conditions (i.e., in ~30,000 ℓ outdoor and ~6400 or ~3800 ℓ indoor Teflon chambers) showed that the reaction was complete in <2-3 minutes (Tuazon et al., 1981, 1982). The major product (~60%) was 1,1-dimethylnitrosamine [$(CH_3)_2NNO$], a potent carcinogen; other significant products included formaldehyde (HCHO), hydrogen peroxide (H_2O_2) and nitrous acid (HONO). The observed products accounted for ~60-70% of the nitrogen in the initial 1,1-DMH, depending upon reaction conditions (Tuazon et al., 1981).

When 2-4 ppm levels of 1,1-DMH were mixed with dry air (4% relative humidity) under dark conditions without ozone in a large outdoor chamber (30,000 ℓ), the approximate half-life was 9 hours (Tuazon et al., 1981). A faster half-life of ~6 hours was observed when air with higher humidity (15%) was used. In similar dark decay experiments with higher concentrations of 1,1-DMH (12-13 ppm), half-lives in dry air of 841$\pm$384 hours in a 6400 ℓ indoor chamber (11% RH) and 341$\pm$64 hours in a 3800 ℓ indoor chamber (17% RH) were reported (Tuazon et al., 1982); the half-life in the 3800ℓ chamber with air at 51% RH was 70.9$\pm$9.6 hours. The reason for the influence of humidity upon rate in the above studies is not known. In both of the above studies, the autoxidation of 1,1-DMH produced NH_3 but only

5-10% of the total loss could be accounted for by NH_3 formation; no other products were detected by infrared spectroscopy. Formaldehyde, dimethylhydrazine, dimethylnitrosamine and dimethylnitramine were detected in previous autoxidation studies (Urry et al., 1965; Loper, 1977; Stone, 1977) of 1,1-DMH, but these studies employed conditions that did not approach those in the actual atmosphere; much higher concentrations (i.e., torr vs. ppm) and reaction vessels with high surface to volume ratios with different surface characteristics (i.e., Teflon was not used) were used.

It also appears that 1,1-DMH can be consumed rapidly by hydroxyl radicals in the atmosphere (Pitts et al., 1981). From consideration of data obtained under simulated atmospheric conditions in a 30,000 ℓ outdoor Teflon chamber, a second-order rate constant was estimated that allowed calculation of a tropospheric half-life of ~3 hours. It was further estimated that the half-life may be 2-5 hours longer in pristine atmospheres and <1 hour in polluted urban atmospheres.

1,1-DMH also reacted at a significant rate with NO_2 in the dark (3800 and 6400 ℓ indoor Teflon chambers), but only at a negligible rate with NO, unless NO_2 was also present (Tuazon et al., 1982). When 1,1-DMH and NO_2 were mixed under conditions of excess 1,1-DMH or excess NO_2, the reactions were typically completed in <10 minutes. The reactions of 1,1-DMH and NO_2 yielded mainly nitrous acid and tetramethyltetrazene-2. An unkown product, suspected to be N-nitroso-N,N'-dimethylhydrazine, was additionally found when NO was present. Tuazon et al. (1981) also showed that 1,1-DMH (2 or 7 ppm) reacted with nitric acid (~10 ppm) in the gas phase to form N,N-dimethylhydrazinium nitrate aerosol at a rate that was too fast for measurement by infrared spectroscopy, but no evidence was obtained for a similar reaction between nitrous acid and 1,1-DMH (Tuazon et al., 1982). When

1,1-DMH was mixed with formaldehyde in the gas phase (i.e., ~15 ppm 1,1-DMH and ~6 ppm HCHO or ~6 ppm 1,1-DMH and ~18 ppm HCHO), formation of the corresponding formaldehyde hydrazone occurred but reaction rates were not determined (Tuazon et al., 1982).

The data of Tuazon et al. (1982), discussed previously, indicates that the carcinogen 1,1-dimethylnitrosamine is a major product of the reaction of 1,1-DMH and ozone. It should be noted, however, that dimethylnitrosamine appears to be degraded rapidly via photolysis in the atmosphere (Hanst et al., 1977; Callahan et al., 1979; Tuazon et al., 1982). Hanst et al. (1977) have shown, for example, that the half-life for dimethylnitrosamine vapor in a 25 ft^3 Teflon bag exposed to full sunlight is ~30 minutes. Tuazon et al. (1982) measured a decay rate of 0.175 min^{-1} for the photolysis of dimethylnitrosamine in a 6400 ℓ indoor Teflon chamber with blacklight irradiation; the half-life calculated from this rate constant is ~4 minutes. Tuazon et al. (1982) further estimated that the rate of photolysis is over 3 orders of magnitude higher than its rate of reaction with hydroxyl radicals, and that the rate of reaction with ozone is negligible.

2.2. WATER

Banerjee et al. (1977) determined that the rate of oxidation of 1,1-DMH by dissolved oxygen in lake water at 30°C varied with pH; disappearance half-lives at pH 5, 6, 7, 8 and 9 were 630, 66, 10, 4.5 and 3.9 hours, respectively. Investigation of the kinetics of oxidation in distilled water as a function of cupric ion concentraton showed that the oxidation rate is comprised of a Cu^{+2}- catalyzed as well as an uncatalyzed step. Copper catalysis was not significant at Cu^{+2} concentrations $<1x10^{-6}$ M (~63.5 ppb), a concentration that was reported to be higher than that of the metal ion content in most natural waters (Banerjee et al., 1981).

The half-life of 1,1-DMH in aquatic media was also studied by Braun and Zirrolli (1983). In the absence of microbial degradation and losses due to physical transport processes, the half-life of 1,1-DMH, presumably due to chemical reactions with O_2 and other free radicals, was reported to be 10-14 days in ponds and seawaters. The compound was found to be extremely stable in distilled water. However, the pH of the water was not reported, nor was the effect of pH on the decomposition rate studied by these investigators.

Aeration of dilute aqueous solutions of 1,1-DMH (~6 ppm) resulted in formation of formaldehyde and 1,5,5-trimethylformazan, and aeration of more concentrated solutions (~180-300 ppm) produced tetramethyltetrazene (Banerjee et al., 1981). Significant formation of carcinogenic 1,1-dimethylnitrosamine occurred only at high concentrations of 1,1-DMH; equilibrium 1,1-dimethylnitrosamine formation increased with increasing 1,1-DMH concentration in the 10-60% 1,1-DMH (by volume) range, reached a maximum at 60-80% 1,1-DMH (by volume) and then sharply decreased. The above results indicate that formation of 1,1-dimethylnitrosamine could potentially occur in the vicinity of spills.

Information on oxidation reactions of 1,1-DMH with free radicals in water, particularly peroxy radicals, is not available. Photolysis (see Section 2.1.) and hydrolysis are not expected to contribute to the degradation of 1,1-DMH in water.

The potential for biodegradation of 1,1-DMH in water has not been explored thoroughly, but is difficult to ascertain and may be moot at neutral to basic pH because of the rapid chemical oxidations. Banerjee et al. (1977, 1981) found that 1,1-DMH oxidation proceeded at the same rate in sterile or non-sterile lake water as in pure distilled water. UV spectra of

the nonsterile water indicated, however, that one of the oxidation products (1,5,5-trimethylformazan) was degraded to an unidentified compound that was not observed in the sterile lake water, indicating microbial action.

Kane and Williamson (1983) studied the biodegradation of 1,1-DMH by four cultures of microorganisms ubiquitous in ambient aquatic environments. These included a mixed culture of nitrifying bacteria (Nitrosomonas-Nitrobacter), a single culture of nitrifying bacteria (Nitrobacter), denitrifying bacteria and anaerobic bacteria. When tested aerobically without added nutrients, it was found that 1,1-DMH (100 mg/ℓ) degraded ~10% in 7 days; with typical nutrients added (NH_4^+, NO_2-, NO_3-, PO_4-3, HCO_3-), the aerobic degradation after 7 days was ~20%. The loss of 1,1-DMH during a 6-day bioassay with the anerobic bacteria was reportedly 26%. Toxic levels of 1,1-DMH, defined as the concentration to reduce substrate metabolism by 50%, were estimated to be 19.2, 1160, 9060 and 1790 mg/ℓ for the Nitrosomonas-Nitrobacter, Nitrobacter, denitrifying and anaerobic bacteria, respectively [for the Nitrosomonas-Nitrobacter and Nitrobacter populations, removal of NH_4^+-N and NO_2^--N, respectively, were assayed; for the denitrifying and anaerobic bacteria, substrate removal was defined in terms of gas production (nitrogen and methane/CO_2, respectively)]. These data indicate that biodegradation of 1,1-DMH may also be limited by compound toxicity.

The significance of evaporation as a transport mechanism for 1,1-DMH in the aquatic media has been studied by a few investigators. A measured evaporation rate for 1,1-DMH from aqueous solution in Petri dishes under conditions of controlled temperatures (21°C) and air velocity (63.5 cm/sec) has been reported to be 13 mg/cm² min (MacNaughton et al., 1979). The significance of this value to actual environmental conditions is unclear

since the concentration of the test solution was not stated, and because the simulation did not adequately represent other parameters such as water depth. It should be noted, however, that the evaporation rate for 1,1-DMH was found to be 100-fold greater than that determined for unsubstituted hydrazine (0.49 mg/cm² min). Stauffer (1977) has reported that a 25% aqueous solution of unsubstituted hydrazine under the same conditions in Petri plates lost ~8% due to evaporation in the first 6 hours and ~21% in the following 4.8 days. Other experiments with unsubstituted hydrazine indicated that evaporation increases at higher concentrations and in the presence of sunshine (due to thermal rather than photochemical effects). Evaporation may be minimal at ppm concentrations due to the miscibility of 1,1-DMH, but experimental data at low concentrations are not available.

The data of Banerjee et al. (1981) presented previously indicate that dimethylnitrosamine could result from oxidation of concentrated aqueous solutions of 1,1-DMH. Dialkylnitrosamines have been reported to be relatively stable toward photolysis in neutral and basic aqueous solutions, and photolabile only under acidic conditions (ERC, 1977; Callahan et al., 1979). Polo and Chow (1976) demonstrated, however, photolytic decomposition of dimethylnitrosamine (initial concentration 74 mg/ℓ) in aerated distilled water that exhibited zero-order kinetics and a half-life of 79 hours. MacNaughton and Stauffer (1975) reported a half-life of ~3 hours for the photolysis of aqueous dimethylnitrosamine (200 mg/ℓ) when exposed to sunlight in covered Petri dishes, but the distilled water used in this experiment may have been slightly acidic due to adsorption of atmospheric CO_2 and a lack of buffering capacity. These data suggest that the most probable fate of dimethylnitrosamine in water is slow photolytic degradation (Callahan et al., 1979). In the absence of light, dimethylnitrosamine could

have an appreciable lifetime; Tate and Alexander (1975) reported that dimethylnitrosamine (20 mg/ℓ) persisted without change due to oxidation, hydrolysis or biodegradation in lake water (pH 8.2) over a period of 3.5 months. Hydrolysis is expected to occur only at elevated temperatures in strongly acidic solutions, and volatilization and sorption do not appear to be important transport mechanisms (Callahan et al., 1979).

2.3. SOIL

The fate and transport of 1,1-DMH in soil has not been extensively investigated. Data summarized in Sections 2.1. and 2.2. indicate that 1,1-DMH released to the soil would be oxidized rapidly by gaseous oxygen or oxygen that is dissolved in soil water. In areas of high concentrations, as in the case of spills, the ready solubility of 1,1-DMH in water suggests that leaching of unevaporated compound could occur.

The adsorption and leaching characteristics of 1,1-DMH in different soils was studied by Braun and Zirrolli (1983). These investigators used pure sand (100% sand), two natural soils and a 1:9 mixture of a natural clay soil and sand for these experiments. In pure sand, no adsorption of 1,1-DMH was observed and almost 100% of the compound could be leached with water from a 20 cm column. In the three other soils, the adsorption of 1,1-DMH varied from 26-80%. Of these total amounts of adsorbed 1,1-DMH, 11-50% remained unrecovered (after elution with 0.1 N HCl), presumably due to reactive processes in the soil. The leaching of 1,1-DMH with water from the three soils varied from 7.2-42.5%. No discernible correlation between leachability and either the soil pH or the soil organic content could be found.

It is evident from the previous discussion that 1,1-DMH may undergo substantial reactions in soils and a substantial amount of this compound may

leach from soil to groundwater. However, the correlation between these behaviors with the particular soil characteristics have not been firmly established.

Dimethylnitrosamine could potentially be formed from 1,1-DMH and come into contact with soil at spill or dump sites (see Section 2.2.). A low octanol-water partition coefficient (log K_{ow} = 0.06) and complete miscibility with water indicate that dimethylnitrosamine may not be sorbed to organic or clay particles (Callahan et al., 1979) and would probably be subject to leaching. Dean-Raymond and Alexander (1976) observed that dimethylnitrosamine exhibited the same mobility as sodium chloride in a column of wet Williamson silt loam. Microbial degradation of dimethylnitrosamine in soil may occur slowly over a period of several weeks to months (Tate and Alexander, 1975; Oliver et al., 1979; Mallik and Tesfai, 1981).

3. EXPOSURE

Monitoring data for 1,1-DMH in air, water or food were not found in STORET or in the available literature (see Appendix A). The high reactivity of 1,1-DMH indicates that this compound will be rapidly degraded via chemical pathways in the environment and that ambient exposure may be negligible.

Small amounts of 1,1-dimethylnitrosamine have been detected in the atmosphere, particularly in polluted air (ERC, 1977). The dimethylnitrosamine is apparently primarily formed from ubiquitous precursors such as amines and nitrogen derivatives (e.g., nitric oxide, nitrogen dioxide, nitrous acid, nitrites, nitrates, and primary, secondary, tertiary and quaternary amines); formation from 1,1-DMH would appear to be negligible. The formation of dimethylnitrosamine in water and soil could also result from the reaction of nitrite with amines, such as those derived from pesticides (ERC, 1977). Dimethylnitrosamine was detected in the air in the vicinity of a Baltimore, MD, 1,1-DMH manufacturing facility (Fine et al., 1977), but the pollution was attributed to production of dimethylnitrosamine as an intermediate rather than degradation of emitted 1,1-DMH. The detection of dimethylnitrosamine in salt water that surrounded the factory (35-940 ng/ℓ), in a drainage ditch on the factory property (5900 ng/ℓ) and in mud puddles immediately adjacent to the factory (200-6000 mg/kg, moist basis) indicates that wet or dry deposition of atmospheric dimethylnitrosamine can occur. Production of 1,1-DMH at this facility ceased in 1976.

4. PHARMACOKINETICS

4.1. ABSORPTION

Limited information is available regarding the absorption of 1,1-DMH by natural routes of exposure. Weeks et al. (1963) reported that six dogs exposed to 1180-7974 ppm 1,1-DMH for ~1 hour retained an average of 83% (range 71-93%) of the inhaled dose. In a dermal absorption study, Smith and Clark (1971) found that application of 300-1800 mg/kg 1,1-DMH to the skin of dogs (3 or 4 per dose) produced detectable blood levels within 30 seconds. Blood levels of 1,1-DMH did not increase during the succeeding 5 minutes, but the greatest increase occurred during the next 25 minutes; thereafter, blood levels rose slowly to a broad peak during the next 1-4 hours. Blood and urine levels of 1,1-DMH were not, however, proportional to dose. It should be noted that the 1,1-DMH exposures in the above experiments elicited toxic responses in the dogs.

Absorption of 1,1-DMH is very rapid following i.p. injection, as evidenced by early high concentrations in the blood (Back et al., 1963) and urine (Section 4.4.). Generally, in experiments with varying doses (5-100 mg/kg) and several species (dogs, cats, rats and monkeys), maximum concentrations of 1,1-DMH in the plasma occurred 15-60 minutes after injection (Back et al., 1963).

4.2. DISTRIBUTION

1,1-DMH is not preferentially concentrated in specific organs in rats following i.p. injection (Mitz et al., 1962) or in rabbits following i.v. injection (Back et al., 1963). Distribution studies following the i.v. administration of 50 mg/kg 1,1-DMH to rabbits indicated that after 2 hours tissue levels became stabilized and the percentage of recovered compound reached a plateau.

4.3. METABOLISM

The metabolism of 1,1-DMH has been characterized incompletely. Injection studies indicate that a large proportion of 1,1-DMH is excreted unchanged in the urine. Analysis of the urine of rats following the i.p. administration of 40 mg/kg of 1,1-DMH showed the presence of parent compound and two major metabolites, but only one of the metabolites was identified. 1,1-DMH and glucose dimethylhydrazone constituted 50-60% and 3-10% of the administered dose, respectively (Mitz et al., 1962). When dogs and cats were injected intraperitoneally with 50 mg/kg 1,1-DMH, simultaneous tracer and colorimetric studies indicated that as much as 30-50% of the dose was excreted in the urine as unchanged compound within the first 5 hours (Back et al., 1963).

Rats given i.p. injections of 40 mg/kg 1,1-DMH have been reported to expire ~2% of the dose after 4 hours (Mitz et al., 1962) or 19% after 7 hours (Reed et al., 1963). NIOSH (1978) has noted that Reed et al. (1963) used larger numbers of experimental animals and a more elaborate system to measure radiolabeled CO_2. Therefore, their data would seem to be more reliable than the data of Mitz et al. (1962). Reed et al. (1963) also found that rats injected intraperitoneally with 20 or 60 mg/kg 1,1-DMH metabolized 23 and 12% of the doses, respectively, to respired CO_2 in 7 hours; 12% of an 11 mg/kg dose was converted and exhaled as CO_2 in 4 hours.

Wittkop et al. (1969) have shown that 1,1-DMH is oxidatively demethylated by rat liver microsome preparations to yield formaldehyde. It was postulated that the production of formaldehyde may result from the demethylation of the tetrazene of 1,1-DMH.

4.4. EXCRETION

The data summarized in Section 4.3. indicate that 1,1-DMH, when administered by injection, is rapidly excreted unchanged in the urine and as CO_2 in the expired air. It was further reported that ~19% of a 40 mg/kg dose intraperitoneally injected into rats was excreted in the urine after 4 hours (Mitz et al., 1962), and that cats given 10 mg/kg intraperitoneally excreted 11-28% of the dose in 6 hours (Back et al., 1963). Reed et al. (1963) found that 43% of an i.p. dose of 11 mg/kg 1,1-DMH was excreted in the urine of rats in 4 hours.

The extent of biliary and/or fecal elimination of 1,1-DMH is unknown.

5. EFFECTS

5.1. CARCINOGENICITY

Continuous lifetime administration of 1,1-DMH in the drinking water (0.1%) of male and female Swiss albino mice produced elevated incidences of angiosarcomas, pulmonary adenomas or adenocarcinomas, malignant lymphomas, kidney adenomas and hepatomas (males only) (Toth, 1972, 1973). The design and results of this study are detailed in Table 5-1. When the data from both sexes are combined, the incidences for the above tumors in treated and control rats were 79 and 2.7%, 71 and 11.4%, 8 and 8.2%, 10 and 0%, and 6 and 0%, respectively. The blood vessel sarcomas were localized primarily in the liver (78/100 treated mice), although lower frequencies were observed in the muscle (18/100), heart (11/100), lungs (7/100) and other tissues.

Syrian Golden hamsters similarly exposed to 0.1% 1,1-DMH in the drinking water developed excess numbers of tumors in the cecum and blood vessels (Table 5-2) (Toth, 1977). The blood vessel tumors developed predominately in the livers of the treated males; angiosarcomas developed in the livers in 11 of the 14 blood vessel-tumor bearing hamsters.

Female Swiss mice given daily doses by gavage of 0.5 mg 1,1-dimethylhydrazine in water, 5 days/week for 40 weeks, developed a significantly increased incidence of lung tumors (Roe et al., 1967). The incidence of lung tumors in animals dying between 40 and 50 weeks was 1/8 as compared to 2/37 for controls; in those animals dying between 50 and 60 weeks, the incidence of lung tumors was 4/9 as compared to 6/42 for controls. The resultant lung tumors, however, were alveologenic or bronchiologenic adenomas or adenocarcinomas, all of which frequently occur spontaneously in mice. No other types of tumors attributable to treatment were observed.

TABLE 5-1

Summary of Oral Carcinogenicity Study of 1,1-Dimethylhydrazine in Swiss Albino Mice[a,b]

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
M	0.01%[c]	life (65 weeks)[d]	life (65 weeks)[d]	NR	drinking water	blood vessels	anglosarcoma	42/50
						lung	adenoma or adenocarcinoma	39/50
						lymphatic system	malignant lymphoma	1/50
						kidney	adenoma	9/50
						liver	hepatoma	6/50
M	0.0%	NA	life (120 weeks)[e]	NA	NA	blood vessels	anglosarcoma	2/110
						lung	adenoma or adenocarcinoma	11/110
						lymphatic system	malignant lymphoma	2/110
						kidney	adenoma	0/110
						liver	hepatoma	0/110
F	0.01%[c]	life (75 weeks)[f]	life (75 weeks)[c]	NR	drinking water	blood vessels	anglosarcoma	37/50
						lung	adenoma or adenocarcinoma	32/50
						lymphatic system	malignant lymphoma	7/50
						kidney	adenoma	1/50
						liver	hepatoma	0/50
F	0.0%	NA	life (130 weeks)[e]	NA	NA	blood vessels	anglosarcoma	4/110
						lung	adenoma or adenocarcinoma	14/110
						lymphatic system	malignant lymphoma	16/110
						kidney	adenoma	0/110
						liver	hepatoma	0/110

[a]Source: Toth, 1972, 1973

[b]Only one dose level was administered. Histologic studies were conducted on the liver, spleen, kidneys, lungs and organs showing gross pathologic changes.

[c]Water consumption data indicated that average daily intake of 1,1-DMH was 0.7 mg.

[d]Survival was tabulated every 10 weeks of age; no survivors at 70 weeks of age (treatment week 65).

[e]No surviving untreated males at 120 weeks or females at 130 weeks.

[f]Survival was tabulated every 10 weeks of age; no survivors at 80 weeks of age (treatment week 75).

NA - Not applicable; NR - Not reported

TABLE 5-2

Summary of Oral Carcinogenicity Study of 1,1-Dimethylhydrazine in Syrian Golden Hamsters*

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
M	0.1%	life (90 weeks)	life (90 weeks)	NR	drinking water	cecum	adenomas or adenocarcinomas	15/50
							adenocarcinomas	8/50
						blood vessels	angiomas or angiosarcomas	14/50
							angiosarcomas	11/50
M	0%	life (110 weeks)	life (110 week)	NA	NA	cecum	tumors	0/100
						blood vessels	tumors	0/100
F	0.1%	life (80 weeks)	life (80 weeks)	NR	drinking water	cecum	adenomas or adenocarcinomas	10/50
							adenocarcinomas	6/50
						blood vessels	angioma or angiosarcoma	2/50
							angiosarcoma	1/50
F	0%	life (90 weeks)	life (90 weeks)	NA	NA	cecum	tumors	1/100
						blood vessels	tumors	0/100

*Source: Toth, 1977

NA = Not applicable; NR = Not reported

Liver carcinomas developed in 3 of 20 BD rats (sex not specified) that were treated with 70 mg/kg 1,1-DMH in the drinking water for life (Druckrey et al., 1967). Control data were not reported, but the exposures represented total doses of 82, 60 or 36 g 1,1-DMH/kg bw reflecting 1100, 806 or 540 days of treatment, respectively.

Administration of 325 µg/day 1,1-DMH by stomach tube 5 times/week for up to 45 weeks did not produce tumors in any of 25 males Wistar rats (Argus and Hoch-Ligeti, 1961). Similarly, Kelly et al. (1969) found that the weekly administration of 1,1-DMH by gavage (~53 mg/kg/week) or i.p. injection (~24 mg/kg/week) for 8 weeks did not elicit tumor development in CD-1 mice.

Haun et al. (1979) exposed groups of 400 female C57BL/6 mice, 200 male Fischer 344 rats and 200 male Golden Syrian hamsters by inhalation to 0, 0.05, 0.5 and 5 ppm 1,1-DMH for 6 hours/day, 5 days/week for 6 months; however, the 1,1-DMH that was used was a commercial grade product that contained ~0.12% dimethylnitrosamine as a contaminant.

The mice, rats and hamsters were sacrificed 13.5-14, 12-14 and 6.5-12 months after termination of exposure, respectively, at which time comprehensive histological examinations were performed on all animals according to the National Cancer Institute (NCI) protocols. As detailed in Table 5-3, statistically significant increased incidences of various tumors were found in rats (bronchiolar adenomas, hepatocellular carcinomas, chromophobe adenomas and fibrous histiocytes) and mice (hemangiosarcomas, Kupffer cell sarcomas and malignant lymphomas) exposed to the two higher doses, but not in hamsters. Mean body weights for all groups of rats and hamsters were reportedly depressed in a non-dose-related manner during the exposure phase of the study, but weight data for the mice were not summarized. Mortality during exposure was not attributed to 1,1-DMH exposure.

TABLE 5-3

Summary of Inhalation Carcinogenicity Study of 1,1-Dimethylhydrazine[a,b]

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)[c]
Rats/F344	M	5.0 ppm 6 hours/day x 5 days/week	6 months	18-19 months	commercial grade[d]	vapor	lung	bronchiolar adenoma	8/191 (P=0.05)
							liver	hepatocellular carcinoma	6/188 (P=0.05)
							pituitary	chromophobe adenoma	89/174 (P=0.01)
							skin	fibrous histiocytomas	9/196 (P=0.05)
							pancreas	islet cell adenoma	8/158 (NS)
Rats/F344	M	0.5 ppm 6 hours/day x 5 days/week	6 months	18-19 months	commercial grade[d]	vapor	lung	bronchiolar adenoma	2/182 (NS)
							liver	hepatocellular carcinoma	2/189 (NS)
							pituitary	chromophobe adenoma	72/169 (P=0.01)
							skin	fibrous histiocytomas	6/193 (NS)
							pancreas	islet cell adenoma	12/169 (0.05)
Rats/F344	M	0 ppm (5.0 and 0.5 ppm control)	NA	18-19 months	NA	NA	lung	bronchiolar adenoma	1/196
							liver	hepatocellular carcinoma	0/193
							pituitary	chromophobe adenoma	39/166
							skin	fibrous histiocytomas	1/199
							pancreas	islet cell adenoma	3/132
Rats/F344	M	0.05 ppm 6 hours/day x 5 days/week	6 months	19-20 months	commercial grade[d]	vapor	lung	bronchiolar adenoma	0/192 (NS)
							liver	hepatocellular carcinoma	0/189 (NS)
							pituitary	chromophobe adenoma	76/182 (NS)
							skin	fibrous histiocytomas	0/197 (NS)
							pancreas	islet cell adenoma	3/174 (NS)

TABLE 5-3 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)[c]
Rats/F344	M	0 ppm (0.05 ppm control)	NA	19-20 months	NA	NA	lung	bronchiolar adenoma	5/189
							liver	hepatocellular carcinoma	0/197
							pituitary	chromophobe adenoma	69/171
							skin	fibrous histiocytomas	1/200
							pancreas	islet cell adenoma	0/170 (NS)
Mice/ C57BL6	F	5.0 ppm 6 hours/day x 5 days/week	6 months	19.5 months	commercial grade[d]	vapor	circulatory system	hemangiosarcoma	19/360 (P=0.01)
							hematopoietic system	Kupffer cell sarcoma	8/360 (P=0.05)
								malignant lymphoma	112/360 (P=0.05)
Mice/ C57BL6	F	0.5 ppm 6 hours/day x 5 days/week	6 months	19.5 months	commercial grade[d]	vapor	circulatory system	hemangiosarcoma	3/368 (NS)
							hematopoietic system	Kupffer cell sarcoma	0/366 (NS)
								malignant lymphoma	98/368 (NS)
Mice/ C57BL6	F	0 ppm (5.0 and 0.5 ppm control)	NA	19.5 months	NA	NA	circulatory system	hemangiosarcoma	3/368
							hematopoietic system	Kupffer cell sarcoma	0/368
								malignant lymphoma	98/368
Mice/ C57BL6		0.05 ppm 6 hour/week x 5 days/week	6 months	19-20 months	commercial grade[d]	vapor	circulatory system	hemangiosarcoma	8/374 (P=0.05)
							hematopoietic system	Kupffer cell sarcoma	4/374
								malignant lymphoma	02/374
Mice/ C57BL6		0 ppm (0.05 ppm control)	NA	19-20 months	NA	NA	circulatory system	hemangiosarcoma	1/355
							hematopoietic system	Kupffer cell sarcoma	1/355
								malignant lymphoma	94/355

TABLE 5-3 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)[c]
Hamster/ Golden Syrian	M	5.0 ppm or 0.5 ppm 6 hours/day, 5 days/week	6 months	12.5 months	commercial grade[d]	vapor	Statistically significant ($p<0.05$) increased incidences of tumors at any site were not found when compared with unexposed controls.		
		0.05 ppm 6 hours/day, 5 days/week	6 months	17-18 months	commercial grade[d]	vapor			

[a]Source: Haun et al., 1979

[b]Multiple dose levels and large number of animals were used, but the exposures were only 6 months in duration. Comprehensive histological examinations were performed, but the test product was contaminated with low levels of a known carcinogen. A separate concurrent set of control animals was provided for the 0.05 ppm test as it was not started at the same time as the 5 and 0.5 ppm experiments.

[c]Statistical significance was determined using the Fisher Exact Test.

[d]The 1,1-DMH that was used was a commerical product that contained 0.12% dimethylnitrosamine.

NA = Not applicable; NS = Not significant

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5.2. MUTAGENICITY

Mutagenicity studies of 1,1-DMH are summarized in Table 5-4. The overall weight of evidence from a variety of microbial and mammalian assays indicates that 1,1-DMH should be regarded as mutagenic.

Numerous Salmonella/Ames assays have been conducted with and without S-9 metabolic activation. The results were generally inconsistent, although it appears that most of the positive responses (reversion to histidine independence) were obtained with strain TA98, a frameshift mutant (Bruce and Heddle, 1979; Parodi et al., 1981; de Flora, 1981). Reverse mutation tests using E. coli WP2 tryptophan auxotroph without activation were negative (Von Wright and Tikkanen, 1980; Hemminki et al., 1981; Brusick and Matheson, 1976), although differential growth inhibition was observed with wild-type (rec^+) and DNA repair-deficient (rec^-) strains of E. coli and B. subtilis (Suter and Jaeger, 1982), indicating direct lethal or mutagenic interaction of 1,1-DMH with bacterial DNA. In tests with yeast, 1,1-DMH did not induce mitotic recombination in S. cerevisiae D4 when tested with or without metabolic activation (Brusick and Matheson, 1976), although point mutations (8-azaguanine resistance and induction of methionine supressors) were induced in A. nidulans (Bignami et al., 1981).

In mutagenesis assays with cultured mouse lymphoma (L5178Y) cells, 1,1-DMH caused forward mutation to thymidine resistance (Brusick and Matheson, 1976; Rogers and Back, 1981), but not to ouabain, thioguanine or cytosine arabinoside resistance (Rogers and Back, 1981). Unscheduled DNA synthesis occurred in human embryonic lung cells that were treated in vitro (Brusick and Matheson, 1976), and in vivo exposure to 1,1-DMH inhibited testicular DNA synthesis in mice (Seiler, 1977). In vivo treatment of mice also caused DNA fragmentation in liver and lung cells (Parodi et al., 1981),

TABLE 5-4

Mutagenicity Testing of 1,1-Dimethylhydrazine

Assay	Indicator Organism	Concentration	Application	Activation	Response	Reference
Reverse mutation (his$^+$)	S. typhimurium G-46, TA1530, TA1535	<2.5x10^2 µmol/mℓ	liquid incubation	+	-	Bartsch et al., 1980
Reverse mutation (his$^+$)	S. typhimurium TA100, TA98	8.3 µmol/plate	plate incorporation	+	+	Bruce and Heddle, 1979
Reverse mutation (his$^+$)	S. typhimurium TA98	21-333 µmol/plate	plate incorporation	±	+ +	Parodi et al., 1981
Reverse mutation (his$^+$)	S. typhimurium TA98	NR	liquid incubation	+	+	Parodi et al., 1981
Reverse mutation (his$^+$)	S. typhimurium TA1530	0.17-0.83 mmol/plate	plate incorporation	-	+	Tosk et al., 1979
Reverse mutation (his$^+$)	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	NR	spiral dilution on surface of top agar or minimal glucose medium	+	+[a]	de Flora, 1981
Reverse mutation (his$^+$)	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	0.01-5.0 µℓ/plate	plate incorporation	+ -	- -	Brusick and Matheson, 1976
Reverse mutation (his$^+$)	S. typhimurium TA100	1.0-50.0 µmol/plate	plate incorporation	+	- -	Von Wright and Tikkanen, 1980
Reverse mutation (his$^+$) (host-mediated)	S. typhimurium TA1950	140 mg/kg, single oral dose	bacteria injected i.p. into mice	NA	-	Von Wright and Tikkanen, 1980
Reverse mutation (tryp$^+$)	E. coli WP2	0.5-2.0 µmol/plate	plate incorporation	-	-	Von Wright and Tikkanen, 1980
Reverse mutation (tryp$^+$)	E coli WP2 uvrA	0.5-2.0 µmol/plate	spot test	-	-	Von Wright and Tikkanen, 1980
Reverse mutation (tryp$^+$)	E. coli WP2 uvrA	six unspecified concentrations	liquid suspension	-	+[b]	Hemminki et al., 1981

TABLE 5-4 (con't)

Assay	Indicator Organism	Concentration	Application	Activation	Response	Reference
Reverse mutation (tryp$^+$)	E. coli WP2 uvrA	0.01-5.0 µl/plate	plate incorporation	+ -	- -	Brusick and Matheson, 1976
Growth inhibition (DNA repair)	B. subtilis rec$^-$/rec$^+$ strains[c]	serial dilutions from limit of solubility	plate incorporation spot test	+ +	+ +	Suter and Jaegar, 1982
Growth inhibition (DNA repair)	E. coli rec$^-$/rec$^+$ strains[d]	serial dilutions from limit of solubility	plate incorporation spot test	+ +	+ +	Suter and Jaegar, 1982
Mitotic recombination	S. cerevisiae D4	0.01-5.0 µl/plate	plate incorporation	+ -	- -	Brusick and Matheson, 1976
Point mutation (8-AG resistance of methionine suppressors)	A. nidulans	0.1-5.0 µl/plate	plate incorporation liquid suspension	- +	- +	Bignami et al., 1981
Forward mutation (TK)	Mouse lymphoma cells (L5178Y)	0.005-0.25 µl/ml	in vitro culture	+ -	+ +	Brusick and Matheson, 1976
Forward mutation (TK)	Mouse lymphoma cells (L5178Y)	0.1-5.0 mM	in vitro culture	-	+	Rogers and Back, 1981
Forward mutation (TdR, TG or Ara-C)	Mouse lymphoma cells (L5178Y)	0.1-5.0 mM	in vitro culture	-	-	Rogers and Back, 1981
Unscheduled DNA synthesis	Human embryonic lung cells (WI-38)	0.1-1.0 µg/ml	in vitro culture	+ -	+ -	Brusick and Matheson, 1976
Inhibition of testicular DNA synthesis	Mice	200 mg/kg	single oral dose	NA	+	Seller, 1977
DNA fragmentation (alkaline elution)	Swiss mice, liver and lungs	250 mg/kg 42 mg/kg/day	single i.p. injection i.p. injejction x 5 days	NA NA	± +	Parodi et al., 1981
Micronucleus	Mice, bone marrow cells (C57BL/6 x C3H/He)F_1	50-500 mg/kg/day	i.p. injection x 5 days	NA	-	Bruce and Heddle, 1979

TABLE 5-4 (con't)

Assay	Indicator Organism	Concentration	Application	Activation	Response	Reference
Sperm abnormality	Mice (C57BL/6 x C3H/He)F_1	50-500 mg/kg/day	i.p. injection x 5 days	NA	-	Bruce and Heddle, 1979
Sperm abnormality	Mice	10-100 mg/kg/day	i.p. injection x 5 days	NA	-	Wyrobek and Bruce, 1975
Dominant lethal	ICR/Ha Swiss mice	25 or 63 mg/kg	single i.p. injection	NA	-	Epstein et al., 1972
Dominant lethal	Mice (male)	1.25, 4.2 and 12.5 mg/kg/day[e]	daily i.p. injection x 5 days	NA	-	Brusick and Matheson, 1976

[a]The positive response was not specficially associated with each tester strain.

[b]*In vitro* alkylation of 4-(p-nitrobenzyl)-pyridine was also demonstrated.

[c]*B. subtilis* strains H17/M45 and HLL3g/HJ-15 were tested.

[d]*E. coli* strains AB1157/JC5547, AB1157/JC2921, AB1157/JC2926 and AB1157/JC5519 were tested.

[e]The high dose corresponds to 1/10 the LD_{50}.

+ = Positive response; ± = Marginally positive response; - = Negative response; NA = Not applicable

but did not induce micronuclei in bone marrow cells (Bruce and Heddle, 1979) or sperm abnormalities (Bruce and Heddle, 1979; Wyrobek and Bruce, 1975). In other tests with mice, single or multiple i.p. injections of 1,1-DMH did not produce dominant lethal mutations (Epstein et al., 1972; Brusick and Matheson, 1976).

5.3. TERATOGENICITY

Teratogenic effects were observed in South African clawed toad larvae, Xenopus laevis, following continuous embryonic exposure to 1,1-DMH concentrations of 2-20 µg/ℓ (Greenhouse, 1976). 1,1-DMH was teratogenic during the neurulation period of embryogenesis, and the malformations affected the head, trunk and tail; the most frequent malformation was tail kinks. The relevance of these findings to mammals is unclear since a non-placental species was used, and the embryos were directly (externally) exposed to the chemical.

5.4. OTHER REPRODUCTIVE EFFECTS

Jeyendran and Graham (1980) found, in an evaluation of potential cryoprotective compounds, that 10% 1,1-DMH was toxic to bovine spermatozoa as determined by progressive motility in yolk extender diluted semen following storage at 5°C for 24 hours.

5.5. CHRONIC TOXICITY

Rinehart et al. (1960) reported that three dogs exposed to 25 ppm 1,1-DMH for 6 hours/day showed signs of CNS toxicity (e.g., depression, salivation and convulsive seizures) after several days of exposure, and hemolytic anemia after 13 weeks (in 2 of 3 survivors). Similar exposure of three dogs to 5 ppm for 26 weeks produced only mild toxic effects (slight lethargy, some hemolytic anemia and slight bilirubinemia). Rats and mice exposed for 6 hours/day to 140 ppm for 6 weeks or 75 ppm for 7 weeks showed

occasional tremors during exposure. At 140 ppm, 29/30 mice and 1/20 rats died, and at 75 ppm, 8/20 mice and 0/30 rats died. The only toxic signs observed in rats at 75 ppm were periods of dyspnea and lethargy, but tonico-convulsions were seen in all exposed rodents that died. With the exception of hemosiderosis in reticuloendothelial system cells in surviving dogs exposed to 25 or 5 ppm 1,1-DMH, treatment-related histopathological alterations were not observed in any of the dogs or rodents.

Back et al. (1978) reported the results of a 6-month inhalation study in which 400 female C57 black mice, 200 male CDF albino rats, 200 male Engle Golden Syrian hamsters and 4 beagle dogs of each sex were exposed for 6 hours/day, 5 days/week to 5, 0.5 or 0.05 ppm 1,1-DMH. No overt signs of toxicity were observed in any of the exposed animals, although non-dose-related depression of weight gain was noted for the rats and hamsters. The results of clinical chemistry tests were normal except for elevated SGPT values (5 and 0.5 ppm) and increased BSP retention (5 ppm) in dogs that returned to normal 6-9 months after exposure ended. Although these findings indicate slight to moderate hepatotoxicity in dogs, it has been shown that the effects may be attributable to dimethylnitrosamine contamination of the 1,1-DMH (Haun, 1967).

Shorter duration subchronic studies in which 1,1-DMH was administered by daily i.p. injection have been conducted. Patrick and Back (1964) injected seven Rhesus monkeys with 10 mg/kg daily, 5 days/week for 4 weeks and observed few effects on clinical parameters (initial weight loss and a 90% increase in plasma glucose level). The only pathologic effects were a slight lipid deposition near the central vein in the liver of one monkey, trace amounts of lipid about the tubular membranes in the kidneys of one monkey, and trace (2 monkeys) to significant amounts (2 monkeys) of lipid in the heart.

Cornish and Hartung (1969) administered daily i.p. injections of 70, 50, 30 or 10 mg/kg 1,1-DMH to groups of 10 rats for 21 days. Doses of ≥30 mg/kg resulted in mortality in the first 3 days (5/10, 6/10 and 9/10 at 30, 50 and 70 mg/kg, respectively) and marked and sustained diuresis. BUN values were increased at 50 mg/kg and a dose-dependent increase in SGOT activity was apparent from 10 mg/kg. Histologic examination showed cloudy swelling and lipid infiltration in the renal tubules of the only surviving animal that received 70 mg/kg/day; less pronounced renal changes were found at 50 mg/kg/day. The apparent NOEL of 10 mg/kg/day is consistent with the study of Back and Thomas (1963), who found no effect on rats after 20 days of i.p. injections at this level.

Peterson et al. (1970) performed routine physical examinations and laboratory tests, including SGPT activity, on Danish Air Force workers who worked with a liquid rocket propellant (1,1-DMH). The concentrations and durations of exposures were not known. It was found that from March, 1961, to January, 1964, SGPT activity was elevated at least once (examinations were performed 3-4 times/year) in 47 (4%) of 1193 persons examined. Liver biopsies performed on 26 of these men showed that 6 specimens were pathological (fatty degeneration) and 5 were uncertain, and that all 6 pathological specimens were from patients that had elevated SGPT at the time of biopsy. There was no follow-up of these workers and it was not possible to confirm that the hepatic effects resulted from exposure to 1,1-DMH, but other conditions known to cause liver damage were ruled out. In an earlier study, positive cephalin flocculation tests were found in five chemical laboratory workers (Shook and Cowart, 1957). The workers were exposed to 1,1-DMH for 10 hours/day, 6 days/week for 3 months and 6-8 times for no more than 4 hours/week for the subsequent 3 months, but the extent of exposure

was not known. Although the above studies suggest that liver damage is a possible effect of exposure to 1,1-DMH in humans, compound related hepatotoxicity cannot definitely be concluded.

5.6. OTHER RELEVANT INFORMATION

Acute inhalation LC_{50} exposures ranging from 24,500 ppm x 5 minutes to 252 ppm x 4 hours for rats (Weeks et al., 1963; Jacobson et al., 1955) and 22,300 ppm x 5 minutes to 981 ppm x 60 minutes for dogs (Weeks et al., 1963) have been reported; Jacobson et al. (1955) further found LC_{50}s of 172 ppm x 4 hours for mice and 392 ppm x 4 hours for hamsters. A single dose oral LD_{50} of 360 mg/kg has been reported for rats (Hodge, 1954). The primary effects of acute exposure to 1,1-DMH are on the CNS (e.g, respiratory difficulties and convulsions), but liver effects have not been reported. It has been reported that 1,1-DMH inhibits glucose catabolism (Reed et al., 1963).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethality of 1,1-DMH was determined in the guppy, Poecilia reticulata (Slonim, 1977). The 24-, 48-, 72- and 96-hour static LC_{50} values, determined in hard water (400-500 mg/ℓ as $CaCO_3$) at 22-24.5°C, were 78.4, 29.9, 17.2 and 10.1 mg/ℓ, respectively. Values reported for soft-water conditions (20-25 mg/ℓ as $CaCO_3$) were 82.0, 45.5, 32.4 and 26.5 mg 1,1-DMH/ℓ, respectively. The compound was more toxic in hard water, more noticeably so at 72 and 96 hours, than in soft water. Slonim (1977) also reported that aeration of the water improved fish survival to a slight degree. The 96-hour LC_{50} value in hard water was 17.5 mg/ℓ when aeration was provided.

Aquatic toxicity testing of 1,1-DMH by the Air Force during the early 1960's was conducted with goldfish, channel catfish, largemouth bass and Daphnia (Heck et al., 1963; Hoover et al., 1964). The 24-hour LC_{50} reported for the fish, in general, was ~30 mg/ℓ, and that for Daphnia was 38 mg/ℓ. A more recent study by the Air Force determined a 24-hour LC_{50} range for guppies to be 10.1-26.5 mg/ℓ (Klein and Jenkins, 1977).

The acute toxicity of 1,1-DMH in two fish species and two crustaceans was reported by Fisher et al. (1980). The 96-hour LC_{50} values for 1,1-DMH in the channel catfish, Ictalurus punctatus, and the golden shiner, Notemigonus crysoleucas, were 11.35 and 34.00 mg/ℓ, respectively. The amphipod, Hyalella azteca, was more sensitive than any of the fish species with a 96-hour LC_{50} value of 4.7 mg/ℓ. The isopod, Asellus sp., was slightly more tolerant than the amphipod, having a 96-hour LC_{50} value of 12.4 mg 1,1-DMH/ℓ.

6.2. CHRONIC TOXICITY

The effects of 1,1-DMH on the embryo and larval development of Xenopus laevis (South African clawed toad) were reported by Greenhouse (1974). Embryos exposed to 1,1-DMH from cleavage stages until hatching at 0, 1, 2, 5, 10 and 20 mg/ℓ resulted in 3, 3, 10, 50, 67 and 100% malformations. Greenhouse (1974) demonstrated, through chronological exposure testing, that the neurulation stage was the most critical period of exposure. The most common abnormalities of exposed embryos and larvae were notochord and head and trunk deformations. Tadpoles exposed to 0.1 and 1.0 mg/ℓ showed no decrease in numbers metamorphosed compared to controls (Greenhouse, 1976). Exposure to 10.0 mg 1,1-DMH/ℓ was lethal to all tadpoles (n = 5). Greenhouse (1977) reported that malformations among embryos exposed from blastula until hatching to 5, 10 and 20 mg 1,1-DMH/ℓ were 40, 52 and 95% of the exposed groups.

6.3. PLANT EFFECTS

The effects of 1,1-DMH exposure for 6, 8 and 10 days on the growth of Dunaliella tertiolecta (marine alga) and Selenastrum capricornutum (freshwater alga) were reported (Harrah, 1977). Testing was conducted in culture media of various nutrient levels. Testing was conducted in culture media containing various dilutions of SAAM, to approximate the nutrient status of oligotrophic (10% SAAM), mesotrphic (33% SAAM) or eutrophic (100% SAAM) conditions. Data on the effective concentration which causes a 50% decrease in growth compared to controls (EC_{50}) and the safe concentration (SC) when no significant growth reduction was noted are reported for the freshwater and marine algae tested at various nutrient levels (Table 6-1). These data suggest that freshwater algae grown in lownutrient media are more susceptible to 1,1-DMH. The tendency for EC_{50} to increase with time may indicate

TABLE 6-1

Toxicity of 1,1-Dimethylhydrazine on Algae*

Species	Duration (days)	Percent SAAM	EC_{50} (mg/ℓ)	SC (mg/ℓ)
Selenastrum capricornutum freshwater	6	10	0.63	4.0
	8	10	1.60	4.0
	10	10	1.60	4.0
	6	33	3.7	0.4
	8	33	5.2	2.4
	10	33	8.3	0.4
	6	100	4.2	0.4
	8	100	6.3	0.4
	10	100	6.3	0.4
Dunaliella tertiolecta marine	6	33	0.73	0.008
	8	33	0.76	0.4
	10	33	0.78	0.008

*Source: Harrah, 1977

SC = Safe concentration; the highest concentration of compound which causes no statistically significant ($P<0.05$) decrease in growth compared with control cultures.

oxidation of 1,1-DMH (see Section 2.2.) and recovery of algal populations. The marine species, D. tertiolecta, was less tolerant of the test compound than the freshwater alga, S. capricornutum.

6.4. RESIDUES

Pertinent data regarding residues of 1,1-DMH in aquatic organisms could not be located in the available literature. However, the complete miscibility of 1,1-DMH with water indicates that its bioconcentration potential is very low or nil, since log BCF is inversely related to the log of water solubility (Kenega and Goring, 1980).

6.5. OTHER RELEVANT INFORMATION

Additional information relevant to the aquatic toxicity of 1,1-DMH could not be located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1978) has recommended that occupational exposure to 1,1-DMH shall be controlled to a ceiling concentration of 0.06 ppm (0.15 mg/m^3), as determined in any 2-hour period. This limit represents the lowest detectable concentration and reflects the judgment that the severity of toxic effects, particularly carcinogenicity, precludes demonstration of a safe level of exposure. ACGIH (1982) currently recommends a TLV-TWA (8-hour/day, 40-hour work week) concentration of 0.5 ppm (1 mg/m^3) for 1,1-DMH; the recommended short-term exposure limit (15-minute TWA) is 1 ppm (2 mg/m^3). The ACGIH (1982) also places 1,1-DMH on the A2 listing as a suspected carcinogen. OSHA (1981) has promulgated that occupational exposure to 1,1-DMH be controlled to an 8-hour TWA concentration of 0.5 ppm. NIOSH (1978), OSHA (1981) and ACGIH (1982) additionally noted that the potential contribution to overall exposure by the cutaneous route may be sufficient if uncontrolled to invalidate the recommended/promulgated limits. The ACGIH (1982) has noted further that West Germany recommends an occupational exposure limit of 0.1 ppm for 1,1-DMH and considers it a potential carcinogen.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 1,1-dimethylhydrazine were not located in the available literature.

8. RISK ASSESSMENT

1,1-DMH appears to be carcinogenic in mice and hamsters by oral administration, but not definitely in rats by this route. A 6-month inhalation study indicated a carcinogenic effect of 1,1-DMH in mice and rats but not in hamsters, but carcinogenicity cannot be definitely attributed to inhaled 1,1-DMH because of the presence of the contaminant dimethylnitrosamine.

In Swiss mice, increased incidences of hemangiosarcomas, pulmonary adenomas or adenocarcinomas, malignant lymphomas, kidney adenomas and liver hepatomas were observed following exposure to 1,1-DMH (~0.7 mg/day) in the drinking water for up to 80 weeks (Toth, 1972, 1973). In another study, female Swiss mice developed an increased incidence of lung tumors when exposed to 0.5 mg/day 1,1-DMH by gavage for 40 weeks (Roe et al., 1967). Weekly administration of ~53 mg/kg 1,1-DMH for 8 weeks by gavage did not, however, induce tumors in CDF1 mice (Kelly et al., 1969). In an inhalation study, exposure to 0.5-5 ppm 1,1-DMH for 6 months produced significantly increased incidences of tumors (hemangiosarcomas, malignant lymphomas, Kupffer cellsarcomas) in C57BL/6 mice (Haun et al., 1979) that were consistent with the types observed in the chronic oral studies.

Administration of 70 mg/day 1,1-DMH in the drinking water for life reportedly produced liver carcinomas in BD rats (Druckrey et al., 1967), but control data were not reported. Administration of 1,1-DMH at a level of 0.3 mg/day by stomach tube for 45 weeks was not tumorigenic for Wistar rats (Argus and Hoch-Ligeti, 1961). In Syrian hamsters, lifetime administration of 1,1-DMH in the drinking water at a concentration of 0.1% produced cecum and blood vessel tumors (Toth, 1977). Inhalation exposure to 1,1-DMH at levels of 0.5-5 ppm for 6 months elicited development of multiple types of tumors in F344 rats (i.e., bronchiolar adenomas, hepatocellular carcinomas,

chromophobe adenomas, islet cell adenomas and fibrous histiocytomas) but tumors were not induced in Syrian hamsters by similar inhalation exposure (Haun et al., 1979).

The previous data are sufficient to classify 1,1-DMH as a carcinogen by the oral route in mice and hamsters. Although the inhalation data should be regarded as equivocal due to the presence of the contaminant carcinogen, the induction of tumors in mice by inhalation can be regarded as corroborative and indicates that the data from the oral study with mice (Toth, 1972, 1973) would be more appropriate for use in quantitative risk estimation. The fact that tumors were induced at a greater number of sites by a lower level of oral exposure in the mice than in the hamsters further supports use of the mouse data for risk assessment. Estimation of the incidences and sites of the various tumors in the mice indicates that the data for induction of hemangiosarcoma in the males would be most suitable for derivation of a carcinogenic potency (q_1^*) factor.

Based on the incidence of angiosarcoma in male Swiss albino mice (Toth, 1972, 1973*) and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a carcinogenic potency factor (q_1^*) of 8.66 $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 1.15×10^{-6} mg/kg/day or 8.05×10^{-5} mg/day for a 70 kg man. Complete data used in deriving the q_1^* are presented in Appendix B.

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*Historical controls (published) were used in the q_1^* determination with this study. The historical controls (2/110) were of sufficient similarity to the unpublished matched controls obtained (3/100) so as to not substantially affect the q_1^* value.

9. REFERENCES

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APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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Some of the carcinogenicity summary tables in this profile were adapted from a report [Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of 1,1-Dimethylhydrazine (57-14-4)] prepared by Syracuse Research Corporation (1983) for the Carcinogen Assessment Group of the U.S. EPA under Contract No. 68-03-3112.

APPENDIX B

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: 1,1-Dimethylhydrazine

Reference: Toth, 1972, 1973

Species, Strain, Sex: mice/Swiss/albino/male

Body Weight: 0.03 kg (assumed)

Length of Exposure (l_e) = 455 days (treated) 840 days (control)

Length of Experiment (L_e) = 455 days (treated) 840 days (control)

Lifespan of Animal (L) = 840 days

Tumor Site and Type: vascular system/angiosarcoma

Route, Vehicle: oral/drinking water

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/No. Tested (or Examined)
0 mg/day	0	2/110
0.7 mg/day	23.3	42/50

Human $q_1^* = 8.66\ (mg/kg/day)^{-1}$

10^{-5} risk level = 1.15×10^{-6} mg/kg/day; 8.05×10^{-5} mg/day for 70 kg man